REMARKS

Before the filing of this Amendment, claims 41-91 were pending in this application, and under examination. Claims 42, 45-46, 49, 52-55 and 57 were previously allowed, but now all claims stand rejected.

By way of this amendment, claims 63-64 and 83-91 are cancelled, and other claims are amended. Reconsideration of the application is respectfully requested.

Interview summary

The undersigned is grateful to Examiners Jon E. Angell and Dave T. Nguyen, and to Biotechnology Practice Specialist Brian Stanton, for the interview held at the Patent Office on September 1, 2004.

The patentability of the claimed invention as it relates to use *in vivo* was discussed extensively. The undersigned explained how the evidence in the file supported applicant's contention that the invention of claims 58-91 can be practiced *in vivo*. The use of hTRT vectors in the rabbit ear model (USSN 10/143,536), and the use of hTR vectors in the paper by Rudolph et al. (Science 287:1253-1257, 2000) provide two demonstrations confirming that the claimed invention is enabled by the specification as filed for *in vivo* use. The Examiners invited applicants to file an expert declaration under 37 CFR § 1.132, explaining the relevance of the Rudolph article. On this basis, it was agreed that if applicants explicitly claimed adenovirus vectors as the mode of therapy for *in vivo* use, then claims generic for different tissue types would be allowable.

The § 1.132 Declaration requested by the Examiners is enclosed with this Response. The remarks that follow explain the logic that underlies applicants' assertion that the invention of claims 58-62 and 65-82 as amended meet all the patentability requirements of § 112 ¶ 1.

Claim amendments

On the recommendation of the Examiners, applicants now include reference in the claims to an amino acid sequence motif. The amendments do not add new matter into the disclosure. Presence of sequences bearing or resembling the "T" motif in functional TRTs of all species is discussed extensively in the text. Reference to the hybridization conditions comes from the definition section occurring in the specification just before the examples.

On the recommendation of the Examiners, claims 45 and 60 have been amended to eliminate reference to *naturally occurring* telomerase reverse transcriptase. Of course, the claims of the application still cover the use of naturally occurring forms of TRT and nucleic acids encoding it, as well as other forms of TRT falling within the claim scope.

Claim 58 has been amended to explicitly refer to an adenovirus vector as a means of delivering the TRT encoding nucleotide sequence into the target cell. Other transfection means can be used, as described in the specification. Applicants reserve the right to reintroduce coverage for more extended coverage in this or any other application in this series.

Amendment to the Specification

Two paragraphs in the Brief Description of the Drawing section have been amended so that the figure references correspond to the figure labels for new FIGS. 10 and 55, which were submitted on May 5, 2004. None of these changes introduces new matter.

Rejections under 35 USC § 112 ¶ 2:

Claim 41 and 58 stand rejected for use of the phrase "a fragment thereof". By way of this amendment, both claims have been reworded so as to remove the phrase objected to.

Withdrawal of this rejection is requested.

Rejections under 35 USC § 112 ¶ 1:

Claims 41-91 stand rejected under the written description requirement of § 112 ¶ 1. The Office Action raises the concern that the claims cover a "vast number" of different sequences, some of which may not have telomerase activity.

Applicants respectfully disagree. The skilled reader can easily make variants based on recombinant DNA technology available at the time of the application, and test them empirically for telomerase activity according to any of the telomerase activity assays or cell proliferation assays described in the application. This is routine functional mapping well within the capabilities of the skilled user. Further, as acknowledged n the Office Action, the application provides additional guidance for motif regions that may participate in the function of the molecule.

The Revised Written Description Guidelines promulgated by the Office indicate that disclosure of a base sequence satisfies the written description requirements of § 112 ¶ 1 for variants exemplified by a prototype sequence and defined by function (Examples 9 and 14). The Examiner

might also be interested in the unpublished decision of the BPAI in the case *Ex parte Yuejin Sun et al.*, where the Board found that a claim for a polynucleotide having at least 80% identity to the prototype sequence was both described and enabled. The claims currently under consideration in this application are in accordance with what is required by the Guidelines.

Withdrawal of this rejection is requested.

Patentability of claims covering use *in vivo*

Claims 41-91 also stand rejected under the enablement requirement of 35 USC § 112 ¶ 1. The Office Action indicates that the specification is enabling for increasing proliferative capacity of a cell *in vitro*, but does not describe or enable use of TRT to increase proliferative capacity of a cell *in vivo*.

Claims 41-57 explicitly refer to increasing cell proliferative capacity *in vitro*, and should therefore not be subject to this rejection.

Claim 58 has been amended to explicitly refer to an *adenovirus* vector as a means of delivering the TRT encoding nucleotide sequence into the target cell. Dependent claims 65-73 (mirrored in claims 74-82) recite particular cell types that are of commercial interest and have been previously shown to be capable of transduction in vivo using adenovirus vectors (as illustrated by the publications filed in this application on February 26, 2003).

For reasons discussed during the interview, applicants respectfully submit that claims of this scope are allowable under the Office's current standard for use of gene therapy vectors *in vivo*.

Here is a roadmap of previous submissions in support of the rationale applicants' position:

- The specification extensively describes the use of TRT for purposes of increasing proliferative capacity of cells (page 110, line 29 ff.; page 118, line 22 ff.).
- Preferred vectors are listed in the specification on page 66, line 5 ff. A model vector is *adenovirus*. The use of adenovirus for increasing cell replicative capacity is illustrated on page 246, line 30 ff.
- The Response filed February 26, 2003, explains how the specification meets the legal requirements for written description and enablement, according to current case law.
- The 37 CFR § 1.132 Declaration by Dr. Calvin Harley explains that successful introduction of a TRT vector *in vivo* will increase the proliferative capacity of cells, the same way it does *in vitro*.
- Dr. Harley also explains that experiments done in the art-accepted rabbit model for ischemic wounds (USSN 10/143,536) shows that TRT improved perfusion in ischemic tissue, attributable to an increase in proliferative capacity of the cells *in vivo*.
- The 37 CFR § 1.132 Declaration by Dr. John Irving explains how someone reading this application at the time it was filed would know how to construct adenovirus vectors such as those used in the rabbit model experiments described by Dr. Harley.

Enclosed with this response as requested by the Examiners is a further Declaration under 37 CFR § 1.132 by Dr. Ed Wirth, Associate Medical Director of Geron Corporation.

Dr. Wirth explains from the position of a medical expert how the article by Rudolph et al. (Science 287:1253-1257) provides further experimental support for the use telomerase-directed adenovirus therapy to increase proliferative capacity of cells *in vivo*. He explains that the adenovirus vectors used by Rudolph et al. supply the missing component of telomerase holoenzyme in mice, just as TRT adenovirus vector therapy would supply the missing component of telomerase holoenzyme in humans.

Animals treated using the Rudolph vector showed increased proliferative capacity of cells in the liver (the target site), which had the therapeutic benefit of making the animals resistant to CCl_4 induced cirrhosis. Dr. Wirth explains how the experiments done in the Rudolph article model human chronic liver disease — specifically, the ability of hTRT encoding vectors to increase proliferative capacity of hepatocytes in the liver of human patients, thereby limiting further damage and allowing the liver cells to regrow.

Both the rabbit ear wound model described in Dr. Harley's Declaration, and the mouse liver cirrhosis model described in Dr. Wirth's declaration, provide experimental confirmation that the TRT adenovirus vectors described and enabled in the subject patent application will work to increase cell proliferative capacity *in vivo*, in accordance with the invention of claims 58-87.

Withdrawal of this rejection is respectfully requested.

Information Disclosure Statement

Applicants previously filed an IDS pursuant to their duty under 37 CFR § 1.56, enclosing a form PTO-1449 with a list of the information being disclosed. Applicants have not yet received a copy of the PTO-1449 initialed by the Examiner to indicate that the information has been made of record in the application.

Accordingly, applicants again request that the information be considered during the examination of this application (if it has not already been considered), and that an initialed PTO-1449 be returned to applicants accompanying a Notice of Allowance or the next Office Action. A copy of the previously filed PTO-1449 is enclosed for the convenience of the Examiner.

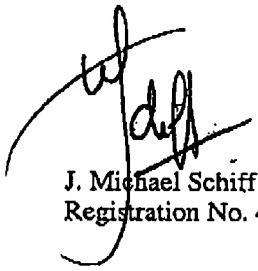
Request for further interview

Applicants respectfully request that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

If after internal review, the Office is still not able to resolve the issue regarding the use of the claimed invention *in vivo*, applicants hereby request a further interview in order to explain the issue further. The Examiner is requested to contact applicants' representative at the telephone number indicated below.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicants hereby petition for such relief. The Commissioner is hereby authorized to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139.

Respectfully submitted,



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